40 CFR Part 799

[OPTS-42034B; TSH-FRL 2815-4]

Identification of Specific Chemical Substance and Mixture Testing Requirements; Ethyltoluenes, Trimethylbenzenes, and the C9 Aromatic Hydrocarbon Fraction

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: The EPA is issuing a final test rule requiring the manufacturers and processors of the C9 aromatic hydrocarbon fraction obtained from the reforming of crude petroleum, other than those who manufacture and process this fraction solely as an impurity, to test the C9 aromatic hydrocarbon fraction for neurotoxicity, mutagenicity, developmental toxicity, reproductive effects, and oncogenicity (unless certain mutagenicity test results are negative). This rule requires that testing of the C9 aromatic hydrocarbon fraction be performed according to protocols submitted to and approved by the Agency.

DATES: These regulations shall be promulgated for purposes of judicial review at 1 p.m. eastern standard time on June 3, 1985. These regulations shall become effective on July 1, 1985.

FOR FURTHER INFORMATION CONTACT: Edward A. Klein, Director, TSCA Assistance Office (TS-799), Office of Toxic Substances, Rm. E-543, 401 M St., SW., Washington, D.C. 20460; Toll Free: (800-424-9065), In Washington, D.C.: (544-1404), Outside the USA: (Operator-202-554-1404).

SUPPLEMENTARY INFORMATION: EPA is promulgating a final rule under section 4(a) of TSCA to require testing of the C9 aromatic hydrocarbon fraction, which contains isomers of ethyltoluene and trimethylbenzene as primary components, for the following health effects: Neurotoxicity, mutagenicity, developmental toxicity, reproductive effects, and oncogenicity (unless specified mutagenicity test results are negative). In its Tenth Report (47 FR 22585, May 25, 1982), the Interagency Testing Committee (ITC) designated mixed ethyltoluenes (ET) and 1,2,4-trimethylbenzene (1,2,4-TMB) for priority consideration for environmental and health effects testing. In its Eleventh Report (47 FR 54624, December 3, 1982), the ITC recommended that the other trimethylbenzenes be considered for testing. EPA issued a proposed test rule published in the **Federal Register** of May 23, 1983 (48 FR 23088) under 40 CFR 799.1625 *C9 aromatic hydrocarbon.* Because of the rearrangement of the specific chemical substances in Part 799, this final rule for the C9 aromatic hydrocarbon is recodified to § 799.2175.

I. Introduction

This notice is part of the overall implementation of section 4 of the Toxic Substances Control Act (TSCA, Pub. L. 94-469, 90 Stat. 2003 *et seq.*; 15 U.S.C. 2601 *et seq.*) which contains authority for EPA to require development of data relevant to assessing the risks to health and the environment posed by exposure to particular chemical substances or mixtures.

Under section 4(a)(1) of TSCA, EPA must require testing of a chemical substance or mixture to develop health or environmental data if the Administrator finds that:

> (A) (i) the manufacture, distribution in commerce, processing, use, or disposal of a chemical substance or mixture, or that any combination of such activities, may present an unreasonable risk of injury to health or the environment,
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> (ii) there are insufficient data and experience upon which the effects of such manufacture, distribution in commerce, processing, use, or disposal of such substance or mixture or of any combination of such activities on health or the environment can reasonably be determined or predicted, and
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> (iii) testing of such substance or mixture with respect to such effects is necessary to develop such data; or
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> (B) (i) a chemical substance or mixture is or will be produced in substantial quantities, and (I) it enters or may reasonably be anticipated to enter the environment in substantial quantities or (II) there is or may be significant or substantial human exposure to such substance or mixture,
>
> (ii) there are insufficient data and experience upon which the effects of the manufacture, distribution in commerce, processing, use, or disposal of such substance or mixture or of any combination of such activities on health or the environment can reasonably be determined or predicted, and
>
> (iii) testing of such substance or mixture with respect to such effects is necessary to develop such data.

For a more complete understanding of the statutory section 4 findings, the reader is directed to the Agency's published proposed test rules on chloromethane and chlorinated benzenes (45 FR 48524; July 18, 1980) and dichloromethane, nitrobenzene, and 1,1,1-trichloroethane (46 FR 30300; June 5, 1981) for in-depth discussions of the general issues applicable to this action.

II. Background

A. Profile

1. *Ethyltoluenes.* Ethyltoluene (ET) occurs in three isomeric forms: 2-ET (ortho), 3-ET (meta) and 4-ET (para). Unless otherwise noted, the term "ethyltoluene" in this document refers to mixed ethyltoluenes, a substance containing all three isomers. ET (CAS No. 25550-14-5) is a colorless liquid readily soluble in most organic solvents, but relatively insoluble in water. ET is sufficiently volatile to enter the atmosphere, and is chemically stable under normal environmental conditions at room temperature. The individual isomers of ET are found in crude oil, gasoline, petroleum products, and have been detected in air and water, and in foods and natural products. ET, along with other nine-carbon aromatic hydrocarbons (C9), is produced during the catalytic reforming of petroleum, which is one of several processes involved in petroleum refining. A portion of this C9 stream is used as a solvent or a component in solvents. The remainder is used in gasoline blending. The solvents produced from the C9 aromatic hydrocarbons are used in paint and varnish formulations, paint thinners, printing inks, pesticide formulations and, to a lesser extent, hydrocarbon lubricating oils for refrigerants. Solvents known to contain significant amounts of ET are Suresol 100®, Aromatic 100® and Espersol 10®.

Nearly pure *ortho*-ET is synthetically produced by Dow Chemical Company and used in the production of *ortho*-vinyltoluene which is used in fiber reinforced polyesters, vinyltoluene alkyds and copolymer resins. Conversion of *ortho*-ET to these products is nearly complete. Mobil Oil Company synthesizes *para*-ET to produce *para*-vinyltoluene.

Total ET production (pure isomers plus that contained in the C9 aromatic hydrocarbon fraction) is estimated to be between 30 to 50 billion pounds annually.

Despite the ITC's designation of ET and the existence of a CAS number, EPA has been unable to identify any product containing only mixed ET isomers. With the exception of the *ortho*-ET manufactured by Dow and the *para*-ET manufactured by Mobil, ET is found exclusively as one of the major components of the C9 fraction.

2. *Trimethylbenzenes.* Trimethylbenzene (TMB) also occurs in three isomeric forms: 1,2,3-TMB, (CAS No. 526–73–8); 1,3,5-TMB, (CAS No. 108–67–8); and 1,2,4-TMB, (CAS No. 95–63–6). The 1,2,4-isomer is the most abundant and commercially is the most important isomer. 1,2,4-TMB is a clear, colorless liquid, readily soluble in organic solvents, but with low solubility in water. It is a stable compound under normal conditions, it undergoes typical electrophilic substitutions such as nitration, halogenation, sulfonation and alkylation, and is oxidized in the presence of catalysts.

Similar to ET, 1,2,4-MB and the other trimethylbenzenes are produced during catalytic reforming and comprise a major portion of the aromatic C9 fraction. The uses of the C9 fraction were discussed in the profile of ET.

1,2,4-TMB is separated from the aromatic C9 reformate by the Koch Refining Company. Koch's 1,2,4-TMB production was in the range of 10 to 50 million lbs in 1977. Current U.S. production volume of isolated 1,2,4-TMB appears to be in excess of 50 million lbs, with imports in 1981 of approximately 11.9 million lbs. Phillips Petroleum Company has reported production only of research quantities of 1,2,4-TMB since 1971.

Most of the isolated 1,2,4-TMB appears to be consumed as a raw material in the manufacture of trimellitic anhydride (approximately 50 million lbs/yr) which is subsequently used in the production of plasticizers, alkyd resins, unsaturated polyesters, and other industrial chemicals.

The 1,2,3-isomer (hemimellitene) is used principally to make a musk, similar to xylene musk. It is also oxidized to anhydro-hemimellitic acid. No information is currently available to EPA on the quantities consumed through these uses, although those quantities are expected to be a small percentage of the total TMB production which is estimated to be approximately 30 billion pounds per year. EPA required reporting under section 8(a) of TSCA to obtain information on the production, exposure and release of 1,2,3- and 1,3,5-TMB (49 FR 25856). No reports have been received by the Agency to date, indicating that there is not substantial production of 1,2,3-TMB. Under the section 8(a) small manufacturer's exemption standards, contained in the Preliminary Assessment Information Rule (47 FR 26992, June 22, 1982), small manufacturers (and importers) were exempt from reporting only if the firm's total annual sales was less than $30 million and less than 100,000 pounds of the chemical were produced or imported per year at a given site.

Some of the 1,3,5-isomer (mesitylene) is separated from the C9 fraction and is used as an intermediate, primarily for production of 1,3,5-trimethyl-2,4,6-tris(3,5-di-tert-butyl-4-hydroxybenzyl) benzene, which is produced by Ethyl Corporation and sold as Ethanox 330®. It is an important antioxidant (noncoloring stabilizer) for plastics such as polypropylene, high-density polyethylene, polyamides, adhesives, specialty rubbers such as Spandex® fibers, and waxes.

B. ITC Recommendations

The ITC designated ET (mixed isomers) and 1,2,4-TMB for priority testing consideration in its Tenth Report, published in the **Federal Register** of May 25, 1982 (47 FR 22585) and recommended in its Eleventh Report published in the **Federal Register** of December 3, 1982 (47 FR 54624) that the other trimethylbenzenes (1,2,3- and 1,3,5-isomers) be considered for testing. These actions were based on the chemicals' exposure potential and the lack of sufficient information on health and environmental effects. The trimethylbenzenes were recommended for testing for neurotoxicity, reproductive effects, teratogenicity and subchronic effects. ET mixed isomers were recommended for testing for mutagenicity, metabolism and subchronic effects. Both ET and TMB were recommended for testing for environmental effects and chemical fate.

C. Proposed Rule

EPA issued a proposed rule published in the **Federal Register** of May 23, 1983 (48 FR 23068) under 40 CFR 799.1625 *C9 aromatic hydrocarbon*, which would require that testing of the C9 aromatic hydrocarbon fraction containing *ortho*-, *meta*-, and *para*-isomers of ethyltoluene and the 1,2,3-, 1,3,5- and 1,2,4-isomers of trimethylbenzene be performed. Because of the rearrangement of the specific chemical substances in Part 799, the final rule for the C9 hydrocarbon fraction is recodified to § 799.2175. Health effects testing proposed for the C9 fraction included neurotoxicity, mutagenicity, teratogenicity (developmental toxicity), reproductive effects, and oncogenicity (unless the results of certain mutagenicity studies are negative). The EPA based its proposed testing requirements on the authority of section 4(a)(1)(B) of TSCA. It found that:

1. There was no production of the mixed ETs aside from production of the C9 aromatic hydrocarbon fraction.

2. There were no data to indicate that exposure to 1,2,4-TMB or other isolated isomers of TMB was substantial and there was no basis for finding that exposure to isolated isomers of TMB may present an unreasonable risk to human health from the effects mentioned by the ITC.

3. There was no evidence of substantial release of isolated TMB isomers to the environment; furthermore, available data were adequate to reasonably predict that these isolated TMB isomers would neither persist nor accumulate in the environment in sufficient quantity that would likely result in an unreasonable risk to the environment.

4. There were substantial amounts of the C9 aromatic hydrocarbon fraction (containing ET and TMB isomers) produced in the U.S. each year (approximately 80 billion pounds).

5. A substantial number of workers and consumers were exposed to the C9 aromatic fraction through exposure to solvents and gasoline.

6. There were insufficient data on neurotoxicity, reproductive effects, teratogenicity, mutagenicity and oncogenicity upon which to reasonably determine or predict the effects of exposure to the C9 fraction, and that testing was necessary to develop such data.

7. EPA did not propose an oncogenic bioassay based on the section 4(a)(1)(B) finding because EPA considered the required mutagenicity tests as an appropriate first tier for oncogenicity. However, EPA found that unless certain of the required mutagenicity tests produced negative results, there would be insufficient basis to rule out the potential of oncogenic effects for the C9 fraction. In such circumstances, EPA found that unless a 2-year bioassay had been conducted, there would be insufficient data upon which to predict oncogenicity, and testing would be necessary to develop oncogenicity data.

8. There were sufficient data on the subchronic effects and metabolism of the C9 fraction; therefore, EPA did not propose testing of these types.

9. Although the C9 fraction was found to be released to the environment in substantial quantities, available data were adequate to predict that this material neither persisted nor accumulated in the environment in

sufficient quantity that would likely result in an unreasonable risk to the environment. For this reason, EPA did not propose that environmental effects testing be conducted at that time.

The scientific support used by EPA in making the proposed section 4 findings and for the proposed test rule was set forth in the support documents for ET and TMB, which are available from the Office of Toxic Substances' TSCA Assistance Office and in the public record for that proposed rule.

III. Public Comment

The comments received by the Agency in response to the proposed rule for ET/TMB/C9 aromatic hydrocarbons were from the American Petroleum Institute (API), the Chemical Manufacturer's Association (CMA), the American Industrial Health Council (AIHC), the Natural Resources Defense Council (NRDC), Eastman Kodak Company, and the Neurobehavioral Toxicity Test Standards Committee of the Division of Psychopharmacology of the American Psychological Association. The major issues identified during the comment period are discussed below.

A. Comments on Substantial Exposure Finding

API commented that the Agency has not demonstrated that there is "substantial exposure" to the C9 aromatic fraction through exposure to motor gasoline. API contended that the Agency's approach to the substantial exposure finding does not satisfy the requirements of section 4(a)(1)(B) of TSCA, violates the Administrative Procedures Act, and yields a conclusion "that a reasoned evaulation of the relevant data will not support." API contended that EPA had not satisfied the statutory requirements of section 4(a)(1)(B) of TSCA in support of a substantial exposure finding for the C9 fraction through exposure to gasoline because it had failed to consider all relevant data available such as: (1) The volatility of the C9 fraction, (2) monitoring studies conducted on C9, and (3) the relevant toxicological data and information available on these compounds.

1. API stated that the term "substantial exposure," where exposure to the C9 aromatic fraction is concerned, is not satisfied by showing simply that a substantial number of workers and consumers are exposed. API cited past EPA regulatory activity on dichloromethane, 1,1,1-trichloroethane and nitrobenzene as instances in which the Agency stated that it was neither feasible nor desirable to make strict numerical definitions of substantial exposure or release, intending rather to make judgments of these factors on a case-by-case basis. It was the opinion of API that the Agency had failed, in the case of C9, to make this individual judgment based on available data which, if considered in the context of section 4 as interpreted by API, would not support the substantial exposure finding.

In the case of C9 in gasoline, the Agency considered both the number of persons potentially exposed as well as the levels and durations of exposure and relevant toxicological data.

The number of persons directly exposed (inhalation, dermal, etc.) to gasoline on a frequently recurring basis, primarily service station attendants (approx. 300,000) and consumers pumping their own gasoline, is certainly large.

Data submitted by industry on exposures to driver-salesmen and service station attendants (Ref. 3) show non-detectable to very low levels of exposures to ET and TMB (92 percent of the readings for ET and TMB are below 0.1 parts per million (ppm)). No data were submitted concerning the levels of ET and TMB exposure to the millions of consumers who pump their own gasoline and are by far the greatest number of individuals exposued to gasoline vapors; however, it is unlikely that the levels of exposure to consumers substantially exceed those for service station attendants. The frequency and extent of dermal exposure of consumers, as well as trained personnel, to gasoline also may constitute an important route of exposure which the industry data do not address.

2. API contended that a reasoned evaluation of existing exposure data demonstrates that exposure to the C9 aromatics through gasoline is not substantial. A reasoned evaluation, API continued, "would consider their relevant physical and chemical properties, like the volatility of the C9s, the monitoring studies conducted on ET, 1,2,4-TMB and others C9s, and relevant toxicological data and information." The API cited volatility data on the C9 fraction, air monitoring data on gasoline vapor concentrations in employee breathing zones at four representative bulk terminals (Ref. 1), service station air sampling at seven representative service stations (Ref. 2), air monitoring data of employees exposed to gasoline in both service station and non-service station settings (Ref. 4), and exposure to gasoline components during typical vehicle refueling operations at gasoline stations (Ref. 4). The last two studies above were new submissions to the Agency. Exposure values in those two studies ranged from non-detectable (ND) to 0.16 ppm for ET and ND to 0.11 ppm for 1,2,4-TMB (detection limit of 0.01 ppm). API stated that these data support the conclusion that exposure to the C9 aromatics through exposure to motor gasoline "occurs at extremely low, indeed barely detectable, levels."

In discussing exposure levels in relation to health effects information, API stated that "an evaluation of the existing toxicity data and information on the alkyl benzenes and the C9 aromatics suggest that excessive concern over the long-term, low level exposure to the C9 aromatics in the complex hydrocarbon mixture is certainly not warranted, as these data indicate the low inherent toxicity of the C9 compounds."

Two subchronic toxicity studies (Refs. 5 and 6) on commercial C9 aromatic solvents (45 to 47 percent TMB; 31 percent ET) previously submitted to EPA were cited by API. API contended that "the absence of clinically significant toxicity at the levels tested in these studies indicates that the C9 aromatics have an extremely low probability of producing chronic effects, particularly at the levels encountered during exposure to gasoline vapor." API further cited the National Academy of Sciences (NAS) review of the toxicity of the alkyl benzenes (Ref. 8), which concluded that chronic toxic effects are unlikely, due to rapid metabolism and excretion. The NAS report further found that although the toxicity of most alkyl benzenes is not well studied, the information available to date on alkyl benzenes in general characterizes these chemicals as "relatively impotent toxic agents" and "not a serious carcinogenic hazard." API concluded that these findings are "strongly supported" by the results of the Shell/Exxon studies (Refs. 5 and 6).

API also noted that "the scores that 1,2,4-TMB and ET received in the TSCA Interagency Testing Committee (ITC) 1980 scoring exercise largely concur with this API position." API stated that in the areas of mutagenicity, carcinogenicity and teratogenicity, ET and 1,2,4-TMB received scores indicating that the ITC had no experimental data in these health effect areas and had little or no reason for suspicion.

The Agency disagrees with API's contention that the Agency has not conducted a reasoned evaluation of existing data and information on exposure to the C9 aromatics through exposures to gasoline. EPA has considered all available data on C9, and believes that information is available

which indicates that a large number of persons are exposed to gasoline, that low levels of C9 are found in vapors of gasoline, and that there is a lack of toxicological data to reasonably determine or predict the significance of those exposures. EPA believes that although the subchronic studies on C9 provide sufficient data to reasonably determine or predict certain chronic effects of C9, these studies do not address adequately the areas of neurotoxicity, reproductive effects, developmental effects, mutagenicity, or oncogenicity to permit the Agency to reasonably determine or predict the effects of C9 exposure in these areas. As the NAS study pointed out, the toxicity of most alkyl benzenes is not well studied.

3. API stated that the Agency's alleged failure to consider all relevant factors would render a final rule defective under the Administrative Procedure Act. API stated that the Agency had "violated the Administrative Procedure Act (APA) by failing to identify the basis for its conclusions that the evidence warranted a section 4 test rule in this case." API described EPA's finding as "a brief two sentences with no supportive or explanatory reasoning." API further stated that the support documents issued for ET and TMB did not articulate a rationale, discuss the factual material EPA found pertinent, discuss all of the relevant evidence, or draw a connection between the facts and EPA's conclusion.

The Agency recognizes the need to explain adequately its basis for regulatory action and believes it has done so in the proposed test rule and this final test rule for the C9 aromatic hydrocarbon fraction. The rulemaking record for this action includes all relevant information considered by the Agency and its analysis of this information.

The support documents issued for ET and TMB discussed the data available to the Agency and the adequacy or inadequacy of these data within the context of section 4. The support documents for ET and TMB provide a more than adequate basis of the Agency's assessment of testing needs based upon review and evaluation of available data pertinent to the chemical substance designated for testing. The ET/TMB support documents discuss the Agency's rationale for its findings and for each proposed test. In the final rule, the Agency is setting forth additional explanation of its findings and the basis for this action.

4. Overall, EPA still believes that there may be substantial human exposure to gasoline and its component hydrocarbons. However, as discussed in Unit III. D. below, the Agency has concluded that data obtained from the toxicological testing of the C9 fraction would have very little relevance to an assessment of the risks of exposure to gasoline. Therefore, EPA is not considering exposure to the C9 fraction through exposure to gasoline as part of its basis for finding substantial human exposure to the C9 fraction. The Agency believes that exposures associated with the manufacture and processing of the C9 fraction and the use of solvents containing significant concentrations of the C9 fraction provide more than sufficient basis for a finding of substantial human exposure under TSCA section 4(a)(1)(B)(i).

B. Comments on the Test Substance

In the proposed rule, the Agency put forth several issues for comment specifically related to the selection of the C9 fraction as the test substance:

1. Is the C9 fraction the appropriate test substance? Can a single C9 substance or mixture be selected which would be representative, for toxicological purposes, of the C9 fraction to which persons are exposed through exposure to solvents and gasoline? If so, what should the specifications be for such a substance or mixture? If not, what substances should be selected for testing and why? Should a commercial C9 fraction be used for testing instead of a synthetic mixture?

API responded that a C9 aromatic solvent could be tested for purposes of assessing unreasonable risk to solvents only and that a blend of the five commercial C9 aromatic solvents would be the most appropriate test article. API strongly emphasized that "the test material recommended by API would not be appropriate for characterizing the hazard from exposure to gasoline." API contended that ET and TMB were only minor components of gasoline and that exposure to ET and TMB vapors from gasoline was likely to be at very low concentrations. The recommended C9 aromatic solvents blend would, according to API, contain the isomers of ET and TMB in proportion relevant to the real world usage of C9 aromatic solvents in the United States.

The Agency agrees that a blend of the five commercial C9 aromatic solvents could serve as an appropriate test article, although the EPA does not believe that such a blend is essential so long as the test substance meets the criteria specified in § 799.2175(b) of the final rule. These criteria require that the test substance have a minimum ET content of 22 percent and a minimum TMB content of 15 percent with minimum total ET/TMB content of 75 percent. Data submitted by API in its comments on the proposed test rule showed a range of 22 to 45 percent ET, 15 to 71 percent TMB and 75 to 90 percent total ET/TMB composition to be representative of the ET/TMB ranges encountered in surveying the major U.S. C9 solvent products currently in use. As discussed in Unit III.D., EPA is no longer concerned with the representativeness of the test substance with respect to exposures resulting from the presence of the C9 fraction in gasoline.

2. The Agency further asked whether testing of the individual ET and TMB isomers should be required for any of the tests? If so, which isomers and which tests.

API commented that the choice of a C9 aromatic solvent to test for certain effects resulting from exposure to such solvents is relevant to making unreasonable risk determination. API stated that it did not believe that the most efficient and accurate method of determining the overall toxicity of a mixture is to test the individual components. API stated that "from a regulatory standpoint, it is often reasonable to assess risk of injury to health or environment for the material to which populations are likely to be exposed (e.g., the C9 solvent)." API noted that testing of representative mixtures has precedence in environmental regulations, citing the 1978 FIFRA guidelines, 40 CFR Part 158, as an example (Ref. 17). Public comments on the FIFRA guidelines recommended that each ingredient of a pesticide product be tested in chronic and subchronic assays, an alternative the Agency considered economically prohibitive, and stated that such testing would not significantly improve the quality of EPA's decision-making.

In the case of the C9 fraction, composed primarily of high percentages of ET and TMB isomers, the Agency agrees that testing the C9 fraction alone would most likely elucidate any potential problems that may result from exposures to the C9 fraction or solvents containing significant concentrations of the C9 fraction. Testing of the individual isomers does not appear necessary at this time in order to evaluate the risk posed by exposure to the C9 fraction and solvents containing it.

C. Comments on Persons Subject to Testing

Comments were received from Eastman Kodak Company concerning the Agency's definition of "manufacture" as that term is used under section 4(a)(1)(B) of TSCA.

Specifically, the comments related that definition to byproducts, impurities and non-isolated intermediates subject to test rules promulgated under section 4. The comments stated that the Agency should clarify in each test rule the potential application of the definition of "manufacturer" to certain persons who might otherwise be required to test, or to reimburse others required to test, because of the unintentional creation of the chemical specified in the rule during manufacture or processing of another chemical substance.

EPA is exempting from these testing requirements those manufacturers and processors which produce and process the C9 aromatic hydrocarbon fraction only as an impurity. The Agency is exempting those manufacturers and processors because the EPA findings under section 4(a)(1)(B) are based on exposures to the C9 fraction which are a result of intentional manufacture, processing, and use. In addition, it will be difficult for both EPA and manufacturers and processors to identify with complete assurance all chemical substances which contain the C9 fraction solely as an impurity. Finally, the Agency would find it difficult to apply both the exemption and reimbursement processes to those who manufacture and/or process the C9 fraction solely as an impurity. The Agency's reimbursement regulations issued pursuant to section 4(c) state that those who manufacture or process chemical substances as impurities will not be subject to test requirements unless the rule specifically states otherwise (40 CFR 791.48b). EPA finds no basis to impose such a requirement in this rule.

Persons who manufacture or process the C9 fraction as a byproduct or as a non-isolated intermediate are subject to the testing requirements set forth in this rule; these activities constitute intentional manufacture and processing of the C9 fraction. The total C9 domestic production, including that produced as a byproduct or a non-isolated intermediate, will be used in determining reimbursement shares under the Data Reimbursement Final Rule. (48 FR 41786).

D. Comments on Relevance of Test Data

API contended that testing of C9 aromatics will not produce data which will enable the Agency to make "unreasonable risk" determinations for persons exposed to gasoline; therefore, EPA does not have a basis for requiring those who manufacture or process gasoline to test the C9 aromatic fraction. The API contends that the data generated by the proposed testing required under section 4 of TSCA must be sufficient to support a comprehensive risk determination that could provide a basis for EPA to take action under TSCA section 6. Because exposure to C9 aromatics is not representative of exposure to gasoline, and because test results on the C9 aromatics will be of minimal value in assessing the risks to persons exposed to low levels of C9 aromatics in gasoline, the Agency should separate its testing of C9 aromatic based on solvent exposures from the questions of risks associated with exposure to gasoline.

API contends that C9 aromatics constitute a minor portion of gasoline vapors, and that data on the biological activity of a small part of a mixture are not useful in predicting the overall effects, let alone the risks, of the mixture. The interaction of chemicals in mixtures can, API states, modify their individual absorption, distribution, metabolism and excretion. Thus, in API's view, the toxicity of an isolated minor component may differ significantly from its toxicity as part of a mixture. In addition, the applicability of the test results on C9 aromatics to assessing gasoline risk will be further complicated by the dilution factor. API stated that, unless a component possesses extreme toxicity, it is rare that it will contribute significantly to the overall risk of the mixture, except additively or synergistically. API contends that the data available on C9 aromatics clearly show no extreme toxicity, and because the testing of this isolated material will not allow one to measure additive or synergistic effects, little is to be gained in the overall risk or hazard evaluation for gasoline exosure by gathering data on isolated C9 aromatics.

EPA does not agree that data required under section 4 must support a comprehensive risk determination, but the Agency does believe that such data must be relevant to that determination. In general, EPA disagrees with API's position that testing of a component or set of components of a mixture or complex substance will not produce data that are relevant to assessing the risk to persons exposed to the tested material as part of the mixture or complex substance. In this instance, however, after reviewing the information available to the Agency, EPA has concluded that test data on the C9 aromatics would only be minimally relevant to assessing the health risks to persons exposed to gasoline. C9 aromatics are among approximately 300 chemical species in gasoline and the levels of C9 encountered in a typical motor gasoline are relatively low (approximately 3 percent). In some cases the testing of a component present at such a level in a complex product may be relevant to assessing the risk of exposure to the complex product (e.g., if the component were found to be a potent neurotoxicant). However, in this instance existing data show unleaded gasoline to be carcinogenic in laboratory animal inhalation studies (Ref. 19). Exposure controls for gasoline are expected to be based on these data or on additional testing of gasoline aimed at characterizing its overall toxicity as a complex product. Data on the C9 aromatic fraction alone will be of minimal relevance to that overall determination. Therefore, EPA is separating its decision to require testing of C9 based on exposure to this material through its manufacture, processing, and use as a solvent from the Agency's broader consideration of testing of gasoline or regulation of gasoline exposures.

API commented further that EPA should reevaluate the economic effect of the proposed test rule for the C9 fraction because test results obtained on C9 aromatics would not be relevant to a determination of the risk of exposure from the C9 aromatics through exposure to gasoline. EPA has performed a revised economic analysis for this final rule based on the test costs and an analysis of the market characteristics of the C9 aromatic solvents. This analysis is discussed in detail in Unit V, Economic Analysis of Final Test Rule.

E. Comments on Protocol Submission and the Phased Test Rule Process

The Natural Resources Defense Council (NRDC) submitted comments concerning the need for requiring validated protocols and recommended modification of the Agency's two-phase test rule process. NRDC stated that the Agency should require test sponsors to use validated reference protocols or give adequate justification for any deviations from these protocols. NRDC cited the Agency's two-phase test rule process (as described at 47 FR 13012; March 26, 1982) as an apparent "reversal" of EPA's previous policy which had required that specific EPA, FIFRA or OECD testing protocols be followed by persons required to test under section 4(a) of TSCA. The proposed policy of demanding only that test sponsors select protocols listed in Agency guidelines, or develop protocols on their own, was cited as an approach "apparently developed in response to industry criticism that the requirements are too rigid and would inhibit innovation in

testing methodologies." The commenter further characterized this decision as compromising the recognized need for reliable and adequate data.

The Agency disagrees with NRDC's view that the two-phase test rule process based on EPA's review and approval of chemical-specific study plans would compromise the ability of the test rule to generate reliable and adequate data. In general, EPA believes that issuance of generic test methodology guidelines, rather than generic test requirements provides more flexibility for test facilities, test sponsors, and EPA itself in arriving at cost-effective, scientifically sound test methodologies, and facilitates the incorporation of scientific judgement where necessary on a chemical-specific basis. This approach also encourages scientific innovation and the development of more sophisticated and scientifically advanced testing methodologies. With either single-phase or two-phase rules a public comment period and an opportunity for a public meeting will allow interested parties to review and comment on the chemical-specific test standards. After this comment period, EPA will issue a final rule adopting chemical specific test standards as required under section 4(b)(1)(B) of TSCA. A more detailed discussion of the Agency's views on these and other related issues may be found in the Agency's Test Rule Development and Exemption Procedures final rule (49 FR 39774; October 10, 1984).

NRDC also stated that the Agency should modify the timing of the two-phase test rule development process so that subsequent test rules, complete with specific protocols for testing, are published within one year of EPA's receipt of the ITC's recommendations. NRDC contended that application of the two-phase rulemaking process in the case of the C9 rule has resulted in the Agency's failure to meet the statutory deadlines for initiating rulemaking.

EPA does not agree that the Agency has not met its statutory responsibility for mixed ET's and 1,2,4-TMB. The Agency's statutory obligation under TSCA section 4(e)(1)(B) was fulfilled with the issuance of the proposed test rule for the C9 fraction; in so doing EPA initiated rulemaking under section 4(a) to require testing appropriate to the actual exposures to mixed ETs and 1,2,4-TMB.

EPA shares NRDC's desire that test rules should be completed as rapidly as possible and the Agency is continuing to explore ways to better achieve that objective. EPA believes that in most instances in the future it will be able to minimize the time required to complete test rulemaking by proceeding in a single phase to propose test standards along with the required tests. Nevertheless, having initiated the rulemaking for the C9 fraction using the two-phase process, EPA believes that the most expeditious way to complete that rulemaking is to continue with the two-phase rulemaking.

F. Comments on Proposed Health Effects Testing

1. *Use of C9 fraction to extrapolate risk for ET/TMB.* In the proposed rule for C9's, the Agency asked whether a negative result or a high no-observed-effect level (NOEL) on the C9 fraction could be used to make reasonable predictions that the individual ET and TMB isomers would not present an unreasonable risk of that effect.

API responded that a negative result (or a high NOEL) for the C9 solvent could be interpreted to mean that it was likely that the individual ET and TMB isomers had no observable effect at the concentration (dose) of the individual isomers administered. API stated that, unlike gasoline, C9 aromatic solvents are composed of substances, i.e., the individual ET and TMB isomers, which boil over a narrow range and are similar in chemical and biological properties. API maintained that the toxicity of such mixtures is generally the sum of that of its individual components, especially for low dose exposure. Therefore, API stated, a determination of the toxicity from exposure to C9 solvents allows inference that its individual components would manifest similar toxicity.

The Agency agrees with API that assessing the toxicity of the C9 mixture as a complete entity should provide a reasonable upper bound for the toxicity of the individual ET TMB in the C9 mixture. (API reported the total percentage ET/TMB content of representative U.S. C9 solvent at 75–90 percent; with a median of 80 percent).

2. *Route of exposure for test article.* The Agency also asked what the routes of exposure for the test substance should be.

API believed that the question related directly to the development of test protocols, and therefore should more appropriately reside in Phase II of section 4 rulemaking, as the Agency described in its notice concerning the test rule development process (47 FR 13012, March 26, 1982), wherein the Agency stated that not until Phase II would sponsors be required to develop test protocols. However, if the Agency proceeds to define the route of exposure in Phase I, the general API comment was that, where applicable, if a route other than that expected in humans is used, it should be justified.

The Agency agrees in principle that where possible the route of exposure for testing should reflect that expected to be encountered in the actual exposure situation to be addressed. The Agency believes, however, that when the two-phase test rule process is used it is appropriate to specify the route of exposure in Phase I. EPA considers such specification to be part of defining the effects for which testing is being required, particularly when more than one route of exposure is possible and the Agency is interested in the effects resulting from a particular type of exposure. There generally will be a significant interelationship between the exposures giving rise to the test rule (which are addressed in the Phase I rulemaking) and the appropriate route of exposure for testing. However, should there be questions of the technical feasibility of conducting a test with the preferred route of exposure which come to light only during the development of study plans, these issues will be addressed in the Phase II rulemaking. In the case C9, the Agency believes dermal and inhalation exposures can be expected to occur. The Agency has specified the inhalation route of exposure for testing of C9 because it believes the inhalation route is the predominant route encountered, and the Agency is particularly interested in the effects resulting from inhalation exposure to the C9 fraction.

3. *Neurotoxicity.* Comments were received from the Neurobehavioral Toxicity Test Standards Committee of the American Psychological Association, concurring with the Agency's recommendation for neurotoxicity testing of the C9 fraction as set forth in the proposed rule. The commenter specifically cited the appropriateness of such testing in the case of the C9 fraction, because these types of violatile lipophilic materials can penetrate into and affect the central nervous system. Because the effects of long-term exposure on the structure and function of the nervous system are unknown and are of concern, the comments characterized the proposed testing as desirable for predicting the potential of exposure to C9 to cause adverse effects on behavior and the nervous system.

The Agency agrees with the comment that examination of neurobehavioral toxicity be included in its evaluation of the C9 fraction because such evaluations have been demonstrated to be relevant in assessing the adverse behavioral effects of inhaled gases and

vapors. The Committee commented that the subchronic data collected would not be useful, however, in establishing short-term exposure threshold limit values (STEL–TLV) to protect against acute performance impairment. While the proposed subchronic testing is not specifically designed to determine a STEL–TLV, EPA believes that the conduct of the subchronic study, combined with existing data, will provide sufficient data to reasonably predict the acute neurotoxic effects of the C9 fraction.

API contended that the Shell 90-day inhalation study and the 1-year chronic study submitted in 1982 were adequate to address the neurotoxic effects of the C9 fraction in rodents, and that an additional 90-day study on C9 as proposed by the Agency was not a necessary or cost-effective implementation of section 4 of TSCA.

The Agency proposed that a 90-day subchronic neurotoxicity test, with functional and neuropathologic components, be performed on the C9 fraction for reasons set forth in the ET support document. Although the Shell study was specifically oriented towards the detection of neurotoxic effects, techniques the Agency believes are necessary to specially prepare neural tissue for histopathologic examination were not used in this study. Furthermore, the primary effects seen in both oral and inhalation toxicity were functional changes, which have not yet been adequately studied. Therefore, the Agency is requiring an additional 90-day study to further investigate neurotoxic effects.

4. *Mutagenicity.* API, CMA, and AIHC submitted comments on the proposed mutagenicity testing requirements for the C9 fraction.

a. *Guidelines for human risk assessment from mutagenicity data.* CMA and AIHC stated that EPA should articulate the human health risks to which the mutagenicity test data are intended to relate, and the methodologies by which the data will be used to assess those risks.

EPA is proposing to use its test scheme in two ways: (1) As a screen to determine the need for long-term testing to characterize the oncogenic potential of the C9 fraction; and (2) to determine whether exposure to the C9 fraction may pose a threat to future generations by inducing either heritable gene mutations or chromosome aberrations.

Risk estimates have been made for humans from mutagenicity test results. For gene mutations, for example, data derived from the mouse specific locus test with the antineoplastic drug procarbazine have been used to estimate the risk of human mutations (Ref. 7).

In this example, the spontaneous mutation rate in humans was calculated by estimating the frequency of genetic disease which might result from new mutations. Second, data from radiation experiments in mice were used to extrapolate from increased mutations to obvious skeletal disorders. Third, an estimate was made to extrapolate from this restricted class of disorders to genetic disease in general. The major assumptions here were an assumed equivalency between mice and humans and an assumed equivalency between radiation-induced mutations and those induced by chemicals. The major health impacts estimated in this way will be from autosomal dominant and X-linked recessive syndromes, with negligible impact from other recessive disorders.

Risk estimates for chromosomal aberrations have also been made (Refs. 13 and 14). The heritable chromosome aberration of concern was reciprocal translocation. The majority of conceptuses with such translocations die *in utero*. Using a somewhat limited human data base and experimental work in the marmoset, it was estimated that 2 to 10 congenitally malformed children arise per million conceptuses for each rad of paternal X-ray exposure. If one knows: (1) The spontaneous frequency of translocations in humans and (2) the increase which results from chemical exposure in laboratory mammals, and if one assumes equivalency for rodents and humans and X-rays and chemicals (or knows how to correct for non-equivalency), the Agency believes that one can calculate the increased disease burden resulting from a defined exposure.

The Agency recognizes that all estimates made using such data are gross estimates at best, that many of the assumptions may not be proven valid, and that there is a great dependence on incomplete data bases. Nevertheless, it is the Agency's view that heritable mutation is a serious threat to the health and well-being of the population and that mutagenicity is a valid regulatable health endpoint. The tests that will be required by this test rule should provide a basis for EPA to determine if exposure to the C9 fraction presents a risk of heritable mutation that would warrant control.

CMA also stated that it was premature to require mutagenicity testing until the Agency had adopted scientifically sound guidelines on mutagenicity risk estimation, that the goals of Phase II of the Gene-Tox Program had still not been finalized nor had the conclusions of this program been announced. Phase II's announced goals include an assessment of the strengths and weaknesses of various test systems for human risk assessment, and development of techniques for using experimental data to evaluate mutagenic risks to the human population.

The Agency has updated its guidelines for mutagenicity risk estimation first published in the **Federal Register** of November 13, 1980 (45 FR 74984). These guidelines treat mutagenicity as a separate endpoint from oncogenicity, and provide guidance on how EPA intends to use the results of mutagenicity testing to estimate human risk (49 FR 46314; November 23, 1984). Public comment has been solicited on the updated guidelines, but in the interim they are being used for Agency assessments.

The report of the Goal 8 Subcommittee of the Gene-Tox Program entitled "Evaluation of Existing Mutagenicity Bioassays for Purposes of Genetic Risk Assessment" is presently undergoing prepublication review prior to publication in "Mutation Research Reviews in Genetic Toxicology". In essence, the report states that there is a high degree of correlation between positive responses in lower tier, nongerm cell assays, and those observed in mammalian germ cell assays; it further concludes that these nongerm cell assays may be used to identify potential mammalian mutagens.

These potential mammalian mutagens can be further tested using germ cell assays which confirm their mutagenic potential and allow one to make human risk estimates from the resulting data. This approach is compatible with the testing proposed by the Agency in the C9 test rule in which positive responses in lower tier assays lead to additional testing of presumptive germ cell mutagens in assays for heritable gene mutations (specific locus assay) and chromosomal aberrations (heritable translocation).

The Gene-Tox Program has adequately validated as meaningful and repeatable the tests included in the final C9 rule (Ref. 12). Furthermore, the test sequence has been designed so that one test compliments the others. In its TSCA section 4 program, the Agency uses a standardized sequence and a model set of tests as a starting point in defining the mutagenicity testing scheme for each chemical, but varies the tests used in the sequence when a chemical's properties or data on the test chemical or related chemicals indicate such a need. Commenters have not suggested any modification of the test scheme in their

comments on the proposed rule other than elimination of certain tests as discussed in Units III.F.4.c. through h., below. The Agency believes that its current model test sequence approach is technically defensible and offers sufficient flexibility to address chemical specific issues.

Likewise, the Agency's approach to the identification of mammalian mutagens is compatible with that of the National Academy of Sciences (Ref. 9). Here too, a series of positive responses in lower tier assays leads to designation of a chemical as a potential mammalian mutagen. Mammalian mutagens are confirmed by positive results in assays which measure heritable mutations.

In summary, the Agency feels that there is a consensus in the scientific community on both the need for, and manner of, identifying mammalian mutagens and that its proposed scheme for identifying these agents is in keeping with those recommended by experts in the field of mammalian mutagenesis. Further, while it is recognized that there is, as yet, no generally accepted single methodology for estimating human risk from mutagenic agents, it is the Agency's view that such methodologies do exist and are usable. Therefore, the Agency concludes that it is appropriate at this time to require mutagenicity testing of the C9 aromatic fraction to obtain data with which to perform risk estimates with a view to regulation should the C9 fraction prove to be a mammalian germ cell mutagen.

b. *Automatic triggers in mutagenicity testing scheme.* In the proposed rule, EPA utilized a mutagenicity testing scheme which included three tiers. The Agency proposed that if positive results were obtained in the lower tiers, manufacturers and processors would be automatically required to conduct the next higher level of test(s). Both CMA and AIHC stated that EPA should eliminate automatic triggers in its mutagenicity testing scheme, and adopt instead a scheme which permits assessment of the weight-of-evidence and consideration of alternative testing approaches.

EPA believes the use of automatic triggers is appropriate in certain portions of its mutagenicity testing scheme for the C9 fraction, but has modified its approach in other portions to take into consideration the concerns raised by the commenters. The Agency's rationale for employing a mutagenicity testing scheme utilizing automatic triggers is discussed in part in Unit III.F.4.a., above. In addition, EPA uses the automatic trigger sequence in section 4 rulemaking as a more expedient means of obtaining necessary test data than that afforded by using a stepwise tiering approach, which would rely on evaluation and quantification of a variety of individual test results as a basis for determining if higher-level testing is necessary. Under the Agency's preferred section 4 rulemaking process, test sequences and results which trigger higher level testing are defined before testing sequences are initiated. No additional regulatory actions by EPA are required between testing tiers. Under a stepwise tiered testing arrangement, a new rulemaking describing the next test sequence and interpretation of results would have to be performed for each level in the tiered sequence. This would result in a very time consuming and laborious process of individual rulemaking for individual testing requirements on a step-by-step basis. The Agency does not believe such an approach would be a timely or cost effective use of Agency resources.

Although the Agency believes the use of automatic triggers is suitable for many of the mutagenicity tests in the C9 test rule, the Agency does acknowledge that the incorporation of scientific judgment may be necessary in circumstances where reference data are not as extensive or where a test is more controversial in nature. For instance, because of the limitations, particularly the sensitivity, of the highest tier mutagenicity tests, EPA believes that a step allowing the Agency's judgment as to the need for those tests would be appropriate. As described below, such a decision step has been incorporated in the final rule for the C9 fraction. In contrast, EPA believes that because of the much more extensive reference data available for conducting and interpreting the results of the first and second tier mutagenicity tests it will not be necessary for the Agency to conduct on independent evaluation of the results prior to requiring that higher tier testing be performed.

To incorporate appropriate scientific judgment prior to the use of end-point mutagenicity tests, EPA has decided to utilize automatic triggers between the first and second tier tests, and a "presumptive automatic trigger and opt-out" approach between second tier tests and the final or "end-point" tests in this final test rule for C9 aromatic hydrocarbons. Under this approach, EPA is promulgating a tiered testing scheme for mutagenicity for the C9 fraction with automatic triggers to additional mutagenicity testing. Before the last tier, EPA will hold a public program review if the results of the previous tier test are positive. Public participation in this program review will be either in the form of written public comments or a public meeting. Request for public comments or notification of a public meeting will be published in the **Federal Register.** If, after review of public comment, no change in the test sequence is deemed necessary EPA will provide formal notification to the test sponsor that the next tier test should be conducted. If the Agency believes additional testing is no longer warranted as a result of the earlier test results, public comment, scientific judgment, and other appropriate factors, EPA will issue a proposed amendment to "opt-out" by repealing the existing requirement and, after consideration of public comment on the proposed amendment, issue a final decision whether it will rescind the rule requirement. This approach offers the advantage of allowing the incorporation of scientific judgment based on the weight of the evidence after the initial testing tiers have been completed, while not significantly delaying higher tier testing where it is deemed necessary.

EPA has decided not to use the public program review approach between the lower tier mutagenicity tests for the C9 aromatic hydrocarbon test rule. EPA believes the use of automatic triggers between these tiers is suitable. It should be noted that this does not exclude the public from requesting modifications in the test program. Provisions are available under section 21 of TSCA for the public to petition EPA at any time to amend a rule under section 4.

c. *Sex-linked recessive lethal (SLRL) assay in Drosophila.* API and CMA both submitted comments questioning the applicability of the *Drosophila* SLRL assay to predict heritable genetic effects.

CMA cited several limitations of the *Drosophila* SLRL assay which it considered to be sufficient cause for eliminating this assay from the mutagenicity testing scheme. These limitations include its performance in the International Collaborative Study (Ref. 10); problems with dosimetry; problems with data evaluation because of the occurrence of clusters; differences in metabolism between insects and man; and incomplete data evaluation by the Gene-Tox Work Group on *Drosophila.*

EPA responds to these comments in the reverse order to which they are listed above: (1) The Gene-Tox Work Group report on the SLRL assay is complete and has appeared in the open literature (Ref. 11). The Work Group concluded that one major advantage of the assay is its objectivity in testing for transmissible mutations in a eukaryotic test system. In addition, using a list of carcinogens developed for Phase I of the

Gene-Tox Program, the Work Group found a 90 percent correlation between in vivo carcinogenicity and the SLRL assay. Using a revised carcinogen list developed during the second phase of the Gene-Tox Program, the Phase II Assessment Panel found an 88 percent correlation between results in the SLRL assay and in vivo carcinogenicity.

(2) CMA is correct in stating that there are metabolic differences between insects and humans. However, the Agency considers these differences to be no greater than those between bacteria and humans such as in the Ames assays, and further believes that the in vivo metabolism afforded by *Drosophila* with intact enzyme systems and repair mechanisms is superior to the artifically manipulated in vitro metabolic activation systems used with bacterial and in vitro cell culture systems.

(3) Statistical methodology which allows for the appearance of clusters exists and should be used in evaluating data from the SLRL assay. Such methods are discussed in the Gene-Tox Work Group report (Ref. 11).

(4) Dosimetry is a generic problem in toxicology and is not unique to studies with *Drosophila*. Good toxicologic practices help to minimize this problem which is not a valid reason for eliminating the SLRL assay from the proposed testing scheme. Also, it should be remembered that results from this assay will not be used for quantitative risk assessment, but rather as a qualitative indication of potential mammalian mutogenicity which will be confirmed by subsequent testing.

(5) A review of the data from the International Collaborative Study (Ref. 10) fails to confirm the 27 percent accuracy figure cited by CMA. Six of 17 carcinogens and 8 of 9 noncarcinogens were correctly identified in this study. Overall, 14 of 26 chemicals were correctly identified, which gives an accuracy rate of 53.8 or 54 percent, not 27 percent as stated by CMA.

In summary, EPA believes that the SLRL assay is sufficiently validated to be used as a qualitative indicator of potential mutagenicity and oncogenicity as outlined in its proposed test scheme. This opinion is shared by the NAS Report (Ref. 9), which recommends the use of this assay in a scheme to identify environmental mutagens. In addition, both Phase I and Phase II of the Gene-Tox Program found the SLRL assay to be ready for use in testing programs. The Phase I Work Group found advantages in the use of this assay for both screening and hazard evaluation (Ref. 11). The Phase II report on the developmental status of bioassays in genetic toxicology found that the SLRL assay was one of the ten assays which could be considered as "routine", using as criteria the number of facilities conducting the test, the number of chemicals and chemical classes represented in the Gene-Tox data base, the uniformity of protocol development and the number of assays conducted per year in all facilities (Ref. 12).

d. *Mouse specific locus assay.* CMA and API both opposed the inclusion of the mouse specific locus assay on the grounds that the test is inappropriate for mutagenic risk evaluation due to lack of chemical data to validate the results, and on the grounds that it is not intended for human risk estimation. They further commented that the test is costly, insensitive, and available only in a limited number of testing facilities.

EPA disagrees with the contention that the mouse specific locus test is not intended for human risk estimation. The assay has been used to test for the genetic effects of both chemicals and radiation. This assay is the primary source of the data used by the National Research Council Advisory Committee on Biological Effects of Ionizing Radiation (BIER) and the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (Refs. 13 and 14) to estimate the genetic risk of radiation. EPA is aware that the NAS (Ref. 9) has recommended that assays such as the dominant skeletal and cataract mutation assays be used for human risk estimation because they measure dominant mutations (as opposed to the recessive mutations detected in the mouse specific locus assay) and permit sampling of a larger portion of the genome than does the specific locus assay. EPA further recognizes that the mouse specific locus assay is subject to many of limitations cited by CMA. Nevertheless, it is the Agency's view that the specific locus assay, in spite of its limitations, is suitable for human risk estimation, primarily because its data base of test chemicals exceeds those of the dominant skeletal and cataract mutation assays and because it has been used for risk estimation with both chemicals and radiation. Further, the Agency believes that the limitations cited by CMA for the mouse specific locus assay apply to both the dominant skeletal and cataract mutation assays as they would to most, if not all, assays currently in use for heritable mutations in mammals. These assays are all subject to limitations in number of chemicals that can be tested and the number of facilities which can perform the assay because of the cost, time, and numbers of animals required. They are not intended as screening assays, but rather as confirmatory tests for heritable mutations. They should be considered equivalent in time, cost and facilities needed to those required to perform a two-year assay for oncogenicity.

e. *Cytogenetic assays.* API and CMA both questioned the Agency's rationale in requiring an in vitro cytogenetic assay in the tiered testing sequence, since an in vivo assay is required upon a negative finding in the in vitro test. API cited the in vivo results as a more definitive endpoint in the evaluation of mutagenic effect.

EPA has included both an in vitro and an in vivo cytogenetics assay in its bottom tier of testing to maximize detection of potentially clastogenic agents. An in vitro cytogenetics assays precedes the in vivo cytogenetics assay because it is a easier to perform than the in vivo cytogenetics assay and is conservative of time, resources, money and animals. Further, the Agency is of the opinion that in vitro cytogenetics assays are sufficiently predictive of both carcinogenicity and potential germ-cell mutagenicity that further testing can be triggered as a result of positive results in this assay. However, the Agency also believes that the in vitro test is subject to sufficient limitations, particularly in the use of in vitro metabolic activation systems, that a negative response, particularly one which occurs in the face of technical difficulties with metabolic activation systems or in the face of erratic or narrowly defined toxicity curves, should be confirmed by an in vivo assay. As additional information on these two test systems becomes available, the Agency will continue to consider the need to include in future test rules both in vitro and in vivo cytogenetics assays and may eliminate one or substitute other assays for the ones now required to determine clastogenicity.

f. *Dominant lethal assay.* API stated that the potential for inducing heritable chromosomal damage could be addressed initially in the reproductive studies, rather than through the use of the dominant lethal assay or the heritable translocation assay. EPA does not agree with this assessment. The use of the dominant lethal assay and the heritable translocation assay provides a more definite evaluation of the potential for heritable chromosomal damage than does the reproductive study, which is oriented towards the detection of more generally defined adverse effects.

CMA did not agree with the inclusion of the dominant lethal test as a higher tier assay because, they claimed, it is: (1) Insensitive because of the high

frequency of spontaneous embryonic death, (2) difficult to interpret because death may be caused by nongenetic events; (3) there are strain differences among mice; and (4) the assay measures chromosomal events indirectly.

EPA is aware of the criticisms directed at the dominant lethal assay by CMA. EPA disagrees with the contention that there is a "high" degree of spontaneous embryonic death, although some fetal wastage does occur in the untreated control population. It is for this reason that one should include untreated control animals in each experiment and should compare experimental data both to concurrent and historical control data for the laboratory performing the assay.

Embryonic death may occur as a result of nongenetic events. However, EPA is of the opinion that it is safe to assume death is a result of chemical treatment when it is statistically increased above control levels in the treated population. Further, because chromosomal aberrations are known to result in fetal wastage (Ref. 15), EPA also believes that for a chemical which has been shown to induce chromosomal aberrations either in vitro or in vivo, it is safe to assume that increased fetal death is a result of chemically induced chromosomal aberrations in the treated population. CMA's argument about strain differences in this assay is spurious. Species and strain differences are known to occur in all assays for toxicological effects and are neither unique to the dominant lethal assay nor germane to the rejection of this assay in a testing program.

In summary, EPA considers the dominant lethal assay to be an appropriate second tier assay for chromosomal aberrations because it provides evidence that the chemical in question reaches germ cell tissues where it induces chromosomal aberrations which are transmitted to the next generation. In this context, the NAS also recommends the use of the dominant lethal assay to confirm suspected mammalian mutagenicity (Ref. 9). Once this activity has been confirmed, NAS further recommends the use of the heritable translocation assay for human risk estimation. Recognizing that other assays which provide such evidence are in development, EPA will be reviewing its position on the dominant lethal assay in the future and may require other tests in place of, or in addition to, this assay in other test rules.

g. *Heritable translocation assay.* CMA objected to the use of the heritable translocation assay, primarily on the grounds that it is a research tool unsuitable to use in a testing program. CMA's primary support for this contention is a quote from the Gene-Tox Work Group Report (Ref. 16), which states: "It should be clearly understood that the heritable translocation test is still under development and that it is not ready for wide scale use in testing."

CMA cited an inadequate data base as one of the limitations of this assay, along with high cost, and an insufficient number of available facilities to perform the assay. These are the same limitations CMA applied to the mouse specific locus assay and EPA's response to them is the same as that articulated above for the mouse specific locus assay. In addition, the heritable translocation assay is available in more facilities than the specific locus assay and is not subject to limitations with source and stock of mice. Although the present data base consists of alkylating agents or agents which are converted to alkylators in vivo, EPA agrees with Gene-Tox report which states that the ". . . test appears appropriate when any compound (regardless of class) gives evidence of dominant-lethal and/or cytogenetic effects in germ cells".

EPA feels that CMA has misconstrued the essential meaning of the characterization of this test by the Work Group. The Gene-Tox report referred to use of the assay in a screening program. EPA agrees that this assay should not now, and because of time and cost consideration, most likely will never be, considered to be a part of a screening program for the identification of potential mutagens. Rather, EPA is suggesting that this assay be used to confirm germ cell mutagenesis. The Gene-Tox Report states ". . . its [the heritable translocation assay's] use is in the final phase of the testing program, when mutagenicity to mammalian germ cells is evaluated and data for use in genetic risk assessment are obtained" (Ref. 16). The NAS also recommended that the heritable translocation test be used for human risk estimation once a suspect mammalian mutagen, identified on the basis of results in an in vitro cytogenetics assay, has been confirmed in a dominant lethal assay (Ref. 9).

Finally, CMA has raised a question about the use of negative results for risk estimation in the face of positive results in other test systems. This problem is not unique to the heritable translocation assay but it also a consideration for results from the mouse specific locus test. For the purposes of risk estimation, agents producing negative results in these tests will have to be presumed nonmutagens and risk estimation for mutagenicity will not be performed.

h. *DNA damage assay.* API contended that the Sister Chromatid Exchange (SCE) assay alone should be adequate to identify potential DNA damage in cells.

The Agency agrees that the SCE assay alone is sufficient to identify potential DNA damage from the C9 fraction and has dropped the requirement for a DNA damage assay from the final rule for C9.

5. *Oncogenicity.* EPA requested comment on whether oncogenicity testing of the C9 fraction should be required only if selected mutagenicity tests produce non-negative results, or whether oncogenicity testing should be required immediately on the basis of the TSCA section 4(a)(1)(B) findings.

API commented that there is a very low probability of the C9 fraction to induce an epigenetic oncogenic effect. API stated that "in the absence of any genotoxic mechanisms, there would be no need to consider the C9's as having a high priority need for oncogenicity testing." API supported current Agency efforts in using an appropriate battery of short-term mutagenic tests to prioritize testing for oncogenic effects, but believed neither a positive mutagenic effect nor a substantial exposure finding alone should automatically trigger oncogenicity testing.

CMA objected to the use of rigidly defined battery of tests where a single positive response would trigger a two-year bioassay and proposed instead a scheme where the results of both short-term genotoxicity testing and other relevant information would be considered "in toto" prior to proceeding with a 2-year bioassay. AIHC stated that appropriate screening batteries for potential oncogenicity should be flexible, allowing the exercise of good scientific judgement and the consideration of expanding data bases in selecting assays and interpreting test results.

EPA agrees with API that there is a very low probability of the C9 fraction to induce an epigenetic effect because long-term subchronic toxicity testing (16 months) produced no indication of sustained histopathological changes related to C9 aromatic hydrocarbon exposure. Therefore, EPA is not requiring oncogenicity testing immediately under section 4(a)(1)(B) for the C9 aromatic hydrocarbon fraction. EPA's proposed and final test schemes for oncogenicity testing of the fraction are designed to screen for oncogenic potential of chemical substances which act through genotoxic mechanisms. While the chronic bioassay is, at present, the most appropriate means of confirming and quantifying a chemical's potential to cause oncogenic effects, the Agency believes that several short-term

genotoxicity tests can provide a reasonable screening of the oncogenic potential of the C9 fraction. If all of these tests yield negative results, the likelihood of the C9 fraction being oncogenic is small and the chronic bioassay will not be required. Conversely, if any one of these trigger tests is clearly positive, potential oncogenicity of the C9 fraction is suggested and the chronic bioassay is essential to confirm or deny that potential and provide a basis for judging what oncogenic risk exposure to the C9 fraction may present. The Agency's rationale for selecting specific trigger tests for such screening is discussed further below. Because the selected short-term tests measure different genotoxic events, each of which has been shown to correlate with oncogenicity in a variety of chemicals, even if only one of these tests was positive and all of the others were negatives, EPA believes that the potential for the C9 fraction to be oncogenic would not be sufficiently disproven to warrant foregoing the chronic bioassay, given the substantial exposure to the substance. However, EPA agrees with the commenters that a weight-of-the evidence judgment by the Agency may be necessary should the results from the specified short-term tests be a mixture of negative and equivocal outcomes.

Therefore, EPA is finalizing the rule with triggering of the chronic bioassay if any of the selected short-term tests fails to produce a negative result. If results of one or more tests are clearly positive, EPA will notify the test sponsors to initate the chronic study. However, if mixed negative and equivocal results are obtained, the Agency will review the overall weight of scientific evidence provided by all of the tests. If, in EPA's judgment, that evidence indicates that oncogenicity of the C9 fraction is quite unlikely, the Agency will solicit public comment on whether it should rescind the requirement for the chronic test.

The Agency proposed that a non-negative response in any of several short-term genotoxicity tests be used to trigger oncogenicity testing for the C9 because it believes that a non-negative response in any of these assays provides sufficient basis to establish a concern for potential oncogenicity. These assays were selected because: (1) Except the the *Drosophila* sex-linked recessive lethal assay, all are mammalian in origin; (2) all are known to detect carcinogens with a reasonable degree of accuracy; (3) all measure a defined genetic endpoint; and (4) all are readily available for general testing purposes.

In the final section 4 test rule for the C9, the Agency has adopted a first tier battery which consists of tests for both gene mutations and chromosomal aberrations. Results of these lower tier assays may trigger additional testing, both for oncogenicity and heritable germ cell mutations. If the C9 fraction is nagative in the required in vitro assays for gene mutation (the Ames assay and one or two in vitro assays for specific locus gene mutation in cells in culture) and in both in vitro and in vivo assays for chromosomal aberrations, no further testing for oncogenic potential will be required.

Of the four tests in the lower tier, oncogenicity testing is triggered by non-negative results in three of them: the in vitro assay for gene mutation in cells in culture; the in vitro assay for chromosomal aberrations; and the in vivo assay for chromosomal aberrations. These assays were chosen as triggers because they are mammalian assays which measure known genetic endpoints. Each of these assays also shows an empirical correlation with in vivo oncogenicity.

The overall correlation between results in the three most widely used tests for gene mutation in cells in culture to oncogenicity, as determined by Phase II of the EPA Gene-Tox Program, is 85.9 percent (Ref. 16). Seventy-three of 85 known chemical carcinogens tested in either the Chinese hamster V79 system, the mouse lymphoma L5178Y system, or the Chinese hamster ovary (CHO) system, were correctly identified. On an individual basis, 18 of 22 (81.8 percent) carcinogens tested in the L5178Y system, 12 of 12 (100 percent) tested in the CHO system and 58 of 69 (84 percent tested in the V79 system were correctly identified. EPA feels that there is sufficient evidence to indicate that these assays may be used to trigger an in vivo assay for oncogenicity. EPA is not, at this time, recommending any one cell system. However, as the data base of tested chemicals increases, certain assays may prove to be more appropriate for specific classes of chemicals. EPA will consider such information in its review of study plans submitted during Phase II of this rulemaking.

Likewise, the EPA is not recommending a particular cell system for use in the in vitro cytogenetics assay. For all cell systems conbined, 17 of 22 carcinogens or 77.3 percent were correctly identified. EPA recognizes that this is a limited data base but nonetheless feels that there is sufficient evidence of an empirical correlation of results in these systems to oncogenicity to allow the use of this assay as a trigger for long-term oncogenicity studies and is, in fact, more concerned about the possibility of false negative results with these test systems.

In vitro sister chromatid exchange (SCE) assays show a better correlation with in vivo carcinogenicity; 40 of 41 carcinogens tested, or 97.5 percent, were correctly identified in these assays. However, the Agency was, and still is, reluctant to adopt these tests as direct triggers for oncogenicity testing because neither the mechanistic basis nor the genetic significance of this event is known. However, in light of the high degree of correlation shown by SCE assays with in vivo oncogenicity, the Agency is revaluating its position and may in the future recommened such assays as triggers for oncogenicity testing.

Only 10 carcinogens have been tested in the in vivo cytogenetics assay; nine were correctly identified (REF. 16). In spite of this limited number of chemicals evaluated, EPA believes that this assay is of sufficient significance that a positive response should be used to trigger long-term testing.

The only second tier assay to be used as a trigger for oncogenicity studies is the *Drosophila* sex-linked recessive lethal (SLRL) assay. This assay shows a good correlation with in vivo test results; 67 of 76, or 88.2 percent, of carcinogens tested in this assay were positive (Ref. 16). It measures a genetic event of known significance, and is an in vivo eukaryotic system. It will not serve as a single test trigger since chemicals which are tested in *Drosophila* will first have shown a positive response in another system such as *Salmonella typhimurium* or the SCE assay. EPA feels that this combination of responses is sufficient to warrant in vivo testing for oncogenicity.

8. *Reproductive effects.* API stated that any debate over the issue of whether the 2-generation inhalation reproduction study should be carried through the second generation belongs in the second phase of rulemaking. The Agency agrees that it is more appropriate to address the second generation question in the second phase of rulemaking, but emphasizes that study plans designed for the performance of such studies should reflect OTS test guideline recommendations, which for reproductive effects testing recommend a 2-generation study, or should provide justification why the protocols

submitted differ from those recommended by EPA.

7. *Estimated test costs.* API stated that the Agency's estimated range of test costs is significantly lower than the actual costs industry will incur to perform the battery of tests proposed in the C9 rule.

The Agency acknowledges that the cost of the mouse specific locus test, for example, is in excess of $100,000, not $10,000, as cited in the proposed rule. The Agency has reviewed its estimated range of test costs for the remaining tests required in this rule, and has revised the test cost estimates where appropriate. A complete discussion of test cost estimates is included in Unit V.

IV. Final Test Rule for C9 Aromatic Hydrocarbon Fraction

A. TSCA Section 4 Findings

The EPA is basing the final testing requirements for the C9 aromatic hydrocarbon fraction on the authority of section 4(a)(1)(B) of TSCA.

1. EPA finds that there are substantial amounts of the C9 aromatic hydrocarbon fraction manufactured, processed and sold for use as solvent end products in the U.S. each year (approximately 500 million pounds), and that a substantial number of persons (approximately 20,000) are exposed to the C9 aromatic hydrocarbon fraction through exposure to solvents. Additional persons are or may be exposed during the manufacture and processing of the much larger volume (approximately 70 billion pounds/year) of the C9 fraction which is blended into gasoline and other fuels. The bases for these findings are set forth in the Agency's ET and TMB support documents.

Data submitted to EPA since the publication of the Notice of Proposed Rulemaking (NPRM) for the C9 fraction (48 FR 23088, May 23, 1983) indicate that certain commercial solvents contain substantial concentrations of C9 aromatic hydrocarbons and that the C9 aromatic hydrocarbon content of solvents in general is much greater than originally estimated. API submitted data which represented 80 percent of the domestic production of C9 aromatic solvents, showing a median ET/TMB content of 80 percent, with a range of 75 to 90 percent. One TSCA section 8(d) submission showed a commercial solvent C9 content of 95 percent (Ref. 18).

2. Based on the large number of persons exposed to the C9 aromatic hydrocarbons through the manufacture and processing of the C9 fraction and the use of C9-containing solvents, taking into account the high percentage of C9 in many of those solvents and the use categories and general use patterns of C9 solvents, EPA finds that there is substantial human exposure to the C9 fraction.

3. EPA finds that although there are sufficient data on the subchronic effects and metabolism of the C9 fraction, currently available data are insufficient to allow the Agency to reasonably determine or predict the neurotoxic, reproductive, teratogenic (or, more appropriately, developmentally toxic), mutagenic and oncogenic effects of exposures to the C9 aromatic hydrocarbons resulting from the manufacture and processing of the C9 fraction and the use of C9-containing solvents. EPA finds that testing is necessary to develop such data.

4. EPA has reconsidered those exposures associated with the processing, distribution and use of motor gasoline and has decided not to include such exposures as a part of the basis of its section 4(a)(1)(B) findings to require testing of the C9 fraction. However, manufacturers and processors of the C9 fraction who do so in the course of producing gasoline and other motor or heating fuels are subject to this rule because the Agency's section 4(a)(1)(B)(ii) findings are based on the manufacture and processing as well as on the use of the C9 aromatic hydrocarbon fraction. Thus, in accordance with TSCA section 4(b)(3)(B), both manufacturers and processors of the C9 fraction are subject to the requirements of this rule (see Unit IV. D.)

B. Required Testing

The EPA is requiring that the C9 aromatic hydrocarbon fraction be tested for neurotoxicity, developmental toxicity, mutagenicity, and reproductive effects, and for oncogenicity unless specific mutagenicity test results are negative.

C. Test Substance

EPA is requiring that a C9 petroleum fraction, composed of mixed isomers of ET (22 percent minimum content) and 1,2,4-, 1,2,3- and 1,3,5-TMB (15 percent minimum content), with a total minimum ET–TMB content of 75 percent, be used as the test substance.

D. Persons Required To Test

Section 4(b)(3)(B) specifies that the activities for which the Administrator makes section 4(a) findings (manufacturing, processing, distribution, use and/or disposal) determine who bears the responsibility for testing. Manufacturers are required to test if the findings are based on manufacturing ("manufacture" is defined in section 3(7) of TSCA to include "import".) Processors are required to test if the findings are based on processing. (Section 3(10) of TSCA, defines "process" as the preparation of a chemical substance or mixture, after its manufacture, for distribution in commerce.) Both manufacturers and processors are required to test if the exposures giving rise to the potential risk occur during use, distribution or disposal. Because EPA has found that the manufacture and processing of the C9 fraction and its use in solvents may give rise to substantial exposure, persons who manufacture or process, or who intend to manufacture or process, the C9 aromatic hydrocarbon fraction (other than as an impurity) at any time from the effective date of this test rule to the end of the reimbursement period are subject to this rule. The end of the reimbursement period will be 5 years, or an amount of time equal to that which was required to develop data if more than 5 years, after the submission of the last final report required under the test rule. As discussed in the Agency's Test Rule Development and Exemption Procedures (40 CFR Part 790), EPA expects that manufacturers will conduct testing and that processors will ordinarily be exempted from testing.

Because TSCA contains provisions to avoid duplicative testing, not every person subject to this rule must individually conduct testing. Section 4(b)(3)(A) of TSCA provides that EPA may permit two or more manufacturers or processors who are subject to the rule to designate one such person or a qualified third person to conduct the tests and submit data on their behalf. Section 4(c) provides that any persons required to test may apply to EPA for an exemption from that requirement. The Agency anticipates that the current manufacturers of C9 aromatic hydrocarbon fractions will form the reimbursement pool and sponsor the testing required. Manufacturers and processors who are subject to the testing requirements of this rule must comply with the test rules and exemption procedures in 40 CFR Part 790.

E. Test Rule Development and Exemptions

Test rule development for the C9 aromatic hydrocarbon fraction will be conducted according to the two-phase process described in 40 CFR Part 790. Under the two-phase process, this Phase I test rule is being promulgated for the C9 aromatic hydrocarbon fraction specifying the test substance, the effects for which test data are to be developed

and which persons are subject to the rule. In Phase II, following promulgation of this Phase I test rule, those persons subject to the rule will be required to develop study plans for the development of data pertaining to the effects specified in the Phase I rule or to obtain exemptions from the testing requirements.

This rule for the C9 aromatic hydrocarbon fraction is a final Phase I test rule. Within 30 days from the effective date of this final Phase I test rule, manufacturers subject to this rule must submit to EPA a letter stating their intention to sponsor testing or an application for exemption. Test sponsors must submit their study plans to EPA within 90 days from the effective date of this Phase I test rule. After an opportunity for public comments, EPA will promulgate a rule adopting the study plans, as proposed or modified, as the chemical specific test standards and schedules for the tests required by the Phase I rule. Testing will also be subject to EPA's generic TSCA Good Laboratory Practice (GLP) standards (40 CFR Part 792). Persons who submit study plans will be obligated to perform the tests in accordance with the test standards and schedules developed. Modification to the adopted study plans can be made only with EPA approval.

Processors of the C9 aromatic hydrocarbon fraction subject to this rule, unless they are also manufacturers, will not be required to submit letters of intent, exemption applications or study plans or to conduct testing unless manufacturers fail to sponsor the required tests. The basis for this decision is that manufacturers are expected to pass an appropriate portion of the costs of testing on to processors through the pricing of their C9 aromatic hydrocarbon products.

EPA's final regulations for the issuance of exemptions from testing requirements are in 40 CFR Part 790. In accordance with those regulations, any manufacturer or processor subject to this Phase I test rule may submit an application to EPA for an exemption from submitting study plans and from conducting any or all of the tests required under this rule. If manufacturers perform all the required testing, processors will be granted exemptions automatically without having to file applications.

F. Reporting Requirements

EPA is requiring that all data developed under this rule be reported in accordance with the EPA Good Laboratory Practice (GLP) standards (40 CFR Part 792), published in the Federal Register of November 29, 1983 (48 FR 53922).

EPA is required by TSCA section 4(b)(1)(C) to specify the time period during which persons subject to a test rule must submit test data. These deadlines will be established in the second phase of this rulemaking in which study plans are approved. The procedures for the second phase rulemaking are described in 40 CFR Part 790.

TSCA section 12(b) requires that persons who export or intend to export to a foreign country any C9 aromatic hydrocabon product subject to the testing requirements of this rule notify EPA of such exportation or intent to export. While the results of required testing may not be available for some time, a notice to the foreign government about the export of such substances serves to alert them to the Agency's concern about the substances. It gives these governments the opportunity to request such data that the Agency may currently possess plus whatever data may become available as a result of testing activities. Thus, upon the effective date of this rule, persons who export or intend to export the C9 aromatic hydrocarbon product must submit notices to the Agency pursuant to TSCA section 12(b)(1). For additional information, see 49 FR 45581 (November 19, 1984).

TSCA section 14(b) governs Agency disclosure of all test data submitted pursuant to section 4 of TSCA. Upon receipt of data required by this rule, the Agency will publish a notice of receipt in the Federal Register as required by section 4(d). Test data received pursuant to this rule will be made available for public inspection by any person except in those cases where the Agency determines that confidential treatment must be accorded pursuant to section 14(b) of TSCA.

G. Enforcement Provisions

The Agency considers failure to comply with any aspect of a section 4 rule to be a violation of section 15 of TSCA. Section 15(1) of TSCA makes it unlawful for any person to fail or refuse to comply with any rule or order issued under section 4. Section 15(3) of TSCA makes it unlawful for any person to fail or refuse to : (1) Establish or maintain records or (2) submit reports, notices, notices, or other records required by the Act or any regulations issued under TSCA.

Additionally, TSCA section 15 (4) makes it unlawful for any person to fail or refuse to permit entry or inspection as required by section 11. Section 11 applies to any "establishment, facility, or other premises in which chemical substances or mixtures are manufactured, processed, stored, or held before or after their distribution in commerce. . . ." The Agency considers a testing facility to be a place where the chemical is held or stored and, therefore, subject to inspection. Laboratory audits and/or inspections will be conducted periodically in accordance with the procedures outlined in TSCA section 11 by designated representatives of the EPA for the purpose of determining compliance with the final rule for the C9 aromatic hydrocarbon fraction. These inspections may be conducted for purposes which include verification that testing has begun, that schedules are being met, that reports accurately reflect the underlying raw data and interpretations and evaluations thereof, and that the studies are being conducted according to EPA GLP standards and the test standards established in the second phase of this rulemaking.

EPA's authority to inspect a testing facility also derives from section 4(b)(1) of TSCA, which directs EPA to promulgate standards for the development of test data.

These standards are defined in section 3(2)(B) of TSCA to include those requirements necessary to assure that data developed under testing rules are reliable and adequate, and such other requirements as are necessary to provide such assurance. The Agency maintains that laboratory inspections are necessary to provide this assurance.

Violators of TSCA are subject to criminal and civil liability. Persons who submit materially misleading or false information in connection with the requirement of any provision of this rule may be subject to penalties calculated as if they had never submitted their data. Under the penalty provisions of section 16 of TSCA, any person who violates section 15 could be subject to a civil penalty of up to $25,000 per day for each violation. Intentional violations could lead to the imposition of criminal penalties up to $25,000 for each day of violation and imprisonment for up to one year. Other remedies are available to EPA under sections 7 and 17 of TSCA, such as seeking an injunction to restrain violations of TSCA section 4.

Individuals as well as corporations could be subject to enforcement actions. Sections 15 and 16 of TSCA apply to "any person" who violates various provisions of TSCA. EPA may, at its discretion, proceed against individuals as well as companies themselves. In particular this includes individuals who report false information or who cause it

to be reported. In addition, the submission of false, fictitious, or fraudulent statements is a violation under 18 U.S.C. 1001.

V. Economic Analysis of Final Test Rule

EPA has prepared an economic valuation that examines the cost of the required testing and the potential economic impacts of those costs on the manufacturers and processors of C9 aromatics subject to this rule. The analysis considered four market characteristics of the C9 aromatic fraction: (1) The price sensitivity of demand for the C9 fraction, (2) producer cost characteristics, (3) industry structure, and (4) market expectations. Costs of conducting the health effects tests required in this rule are estimated to range from $1,187,656 to $3,414,369, with annualized test costs ranging from $307,742 to $884,720. Based on these test costs and an analysis of the market characteristics of the C9 aromatic fraction, the economic evaluation indicates that the potential for a significant adverse economic impact is low. This conclusion is based primarily on the following observations:

1. The demand for C9 for solvent use is relatively inelastic due to its selective performance advantage in its major uses.

2. The market expectations for C9 solvents are generally favorable.

3. The relative magnitude of the test cost is small (i.e., an estimated 0.001 cents per pound in the upper bound case); this represents 0.07 percent of the sales value of C9.

VI. Availability of Test Facilities and Personnel

Section 4(b)(1) of TSCA requires EPA to consider "the reasonably foreseeable availability of the facilities and personnel needed to perform the testing required under the rule." Therefore, EPA conducted a study to assess the availability of test facilities and personnel to handle the additional demand for testing programs negotiated with industry in place of rulemaking. Copies of the study, "Chemical Testing Industry: Profile of Toxicological Testing," October, 1981, can be obtained through the NTIS under publication number PB 82-140773.

On the basis of this study, the Agency believes that there will be available test facilities and personnel to perform the testing required in this test rule.

VII. Guidelines and Reports

The following guidelines and reports referenced in this rulemaking are available from the: National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA 22161, (703-487-4650).

NTIS publication No.	Title	Price
PB 83-140773	Chemical Testing Industry: Profile of Toxicological Testing	$16.00
PB 83-257691	OTS Health Effects Test Guidelines—new and revised	25.00
PB 83-233295	OTS Health Effects Test Guidelines—new and revised	11.50
PB 83-153916	Pesticide Assessment Guidelines, Subdivision F—Human and Domestic Animals	16.00

The OECD Guidelines for Testing of Chemicals referenced in this rulemaking are available for $80.00 from: OECD Publications and Information Center, Suite 1207, 1750 Pennsylvania Ave., NW., Washington, D.C. 20006, (202-274-1857).

VIII. Judicial Review

Judicial review of this final rule may be available under section 19 of TSCA in the United States Court of Appeals for the District of Columbia Circuit or for the circuit in which the person seeking review resides or has its principal place of business. To provide all interested persons an equal opportunity to file a timely petition for judicial review and to avoid so called "races to the courthouse," EPA has decided to promulgate this rule for purposes of judicial review two weeks after publication in the **Federal Register**, as reflected in "**DATES**" in this notice. The effective date has, in turn, been calculated from the promulgation date.

IX. Rulemaking Record

EPA has established a public record for this rulemaking (docket number OPTS-42034). This record includes the basic information the Agency considered in developing this proposal, and appropriate **Federal Register** notices. The Agency will supplement the record with additional information as it is received. Confidential Business Information (CBI), while part of the record, is not available for public review. A public version of the record, from which CBI has been deleted, is available for inspection from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays, in Rm. E-107, 401 M St., SW., Washington, D.C.

This record includes the following information:

A. Supporting Documentation

(1) **Federal Register** notices pertaining to this rule consisting of:

(a) Notice of final rule on the C9 aromatic hydrocarbon fraction.

(b) Notice of the proposed rule on ET/TMB and the C9 aromatic hydrocarbon fraction (48 FR 23088).

(c) Notice containing the ITC designation of ET and 1,2,4-TMB to the Priority List (47 FR 22585).

(d) Notice containing the ITC recommendation of 1,2,3- and 1,3,5-TMB to the Priority List (47 FR 54624).

(e) Notice of final rule on EPA's TSCA Good Laboratory Practice Standards (48 FR 53922).

(f) Notice of final rule on test rule development and exemption procedures (49 FR 39774, October 10, 1984).

(g) Notice of final rule concerning data reimbursement (48 FR 41786).

(2) Support documents consisting of:

(a) ET and TMB Technical Support documents.

(b) Economic impact analysis of final test rule for the C9 aromatic hydrocarbon fraction.

(c) Economic impact analysis of NPRM for the C9 aromatic hydrocarbon fraction.

(3) Communications consisting of:

(a) Written public comments.

(b) Summary of telephone conversations.

(c) Meeting summaries.

(4) Reports—published and unpublished factual materials, including contractors' reports.

B. References

(1) *Shell Oil Company 1975.* Air monitoring data on gasoline vapor concentrations in employee breathing zones at four representative bulk terminals. In: Letter from J.P. Sepesi (Shell) to Document Control Officer, OPTS, USEPA, dated July 8, 1982.

(2) *Shell Oil Company 1977.* Service station air sampling at seven representative service stations. In: Letter from J.P. Sepesi (Shell) to Document Control Officer, OPTS, USEPA, dated July 8, 1983.

(3) *Shell Oil Company 1982.* Exposure to driver salemen. In: Letter from J.P. Sepesi (Shell) to Document Control Officer, OPTS, USEPA, dated July 8, 1982.

(4) *API 1983.* Comments on Proposed Test Rule on Ethyltoluenes, Trimethylbenzenes and the C9 Aromatic Hydrocarbon Fraction. Letter from Phil G. Goulding, American Petroleum Institute, to Document Control Officer, OPTS, USEPA, dated Sept. 1, 1983.

(5) *Shell Oil Company 1980.* Report on the inhalation toxicity of SHELLSOL A to rats following 13 weeks exposure. Study No. TGLR.79.176.

(6) *Shell Oil Company 1980.* Report on toxicity of SHELLSOL A/SOLVESSO 100 to rats following daily exposure to vapor atmosphere for 12 months. Study No. SBGR.81.172. (Shell/Exxon joint submission).

(7) *Ehlins, U.H., Neuhouser, A. 1979.* "Procarbazine-induced specific locus mutations in male mice." *Mutation Res* 59:245–256.

(8) *National Academy of Sciences 1981.* "Review of the alkyl benzenes." National Academy Press, Washington, D.C.

(9) *National Academy of Sciences 1982.* National Research Council Committee on Chemical Environmental Mutagens. "Identifying and estimating the genetic impact of chemical mutagens." National Academy Press, Washington, D.C., pp. 141–142.

(10) *de Serres, F.J., Ashby, J. 1981.* "Evaluation of short-term tests for carcinogens." Report of the International Collaborative Program. Elsevier/North Holland. New York. Amsterdam. Oxford.

(11) *Lee, W.R., Abrahamson, S., Valencia, R., von Halle, E.S., Wurgler, F.E., and Zimmering, S. 1983.* "The sex-linked recessive lethal test for mutagenesis in *Drosophila melanogaster.*" A report of the U.S. Environmental Protection Agency Gene-Tox Program. *Mutation Res* 123:183–279.

(12) *Brusick and Auletta. 1984.* "Developmental status of bioassays in genetic toxicology." A report of Phase II of the USEPA's Gene-Tox Program. *Mutation Res.* In Press.

(13) *National Research Council. Advisory Committee on the Biological Effects of Ionizing Radiations. 1972.* The effects on populations of exposures to low levels of ionizing radiation. (BIER I). National Academy of Science, Washington, D.C.

(14) *UNSCEAR. 1977.* United Nations General Assembly. Report of the United Nations Scientific Committee on the Effects of Atomic Radiation. Official records of the General Assembly. Thirty-second session. Supplement No. 40 (A/32/40). United Nations, New York.

(15) *Brewen, J.G., Payne, H.S., Jones, K.P., Preston, R.J. 1975.* "Studies on chemically induced dominant lethality. I. The cytogenetic basis of MMS-induced dominant lethality in post-meiotic germ cells." *Mutations Res* 33:239–250.

(16) *Generoso, W.M., Bishop, J.B., Goss Lee, D.G. Newell, G.W., Sheu, C-J, von Halle, E. 1980.* "Heritable translocation test in mice." *Mutation Res* 76:191–215.

(17) *USEPA. 1978.* Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). 40 CFR Part 58. Guidelines for Registration for FIFRA.

(18) *Marathon Oil Company 1984.* April 2 letter to USEPA. TSCA–8(d) submission (cover letter) on aromatic C9 fraction from petroleum refining.

(19) *API 1983.* September 29. TSCA 8(d) submission No. FYI–AX–1083–0148 (Sequence N). Chronic inhalation of unleaded motor fuel. Dated Sept. 15, 1983 conducted by International Research and Development Corporation, Mattawan, Michigan, 49071.

X. Other Regulatory Requirements

A. Classification of Rule

Under Executive Order 12291, EPA must judge whether a regulation is "major" and, therefore, subject to the requirement of a Regulatory Impact Analysis. The regulation for this chemical substance is not major because it does not meet any of the criteria set forth in section 1(b) of the order. First, the actual annual cost of the testing prescribed for the C9 aromatic hydrocarbon fraction is less than $704,647 over the expected market life of the C9 fraction for use in solvents. Second, because the cost of the required testing will be distributed over a large production volume, the rule will have only very minor effects on producers' costs or users' price for this chemical substance. Finally, taking into account the nature of the market for this substance, the low level of costs involved, and the expected nature of the mechanisms for sharing the costs of the required testing, EPA concludes that there will be no significant adverse economic impact of any type as a result of this rule.

This regulation was submitted to the Office of Management and Budget (OMB) for review as required by Executive Order 12291. Any comments from OMB to EPA, and any EPA response to those comments, are included in the public record.

B. Regulatory Flexibility Act

Under the Regulatory Flexibility Act, (15 U.S.C. 601 *et seq.*, Pub. L. 96–354, September 19, 1980), EPA certifies that this test rule will not have a significant impact on a substantial number of small businesses for the following reasons:

1. There are no small manufacturers of the C9 aromatic hydrocarbon fraction.

2. Small processors are not likely to perform testing themselves, or to participate in the organization of the testing effort.

3. Small processors will experience only minor costs in securing exemption from testing requirements.

4. Small processors are unlikely to be affected by reimbursement requirements.

C. Paperwork Reduction Act

The information collection requirements contained in this rule have been approved by the Office of Management and Budget (OMB) under the provisions of the Paperwork Reduction Act of 1980, 44 U.S.C. 3501 *et seq.* and have been assigned OMB control number 2070–0033.

List of Subjects in 40 CFR Part 799

Testing, Environmental protection, Hazardous material, Chemicals, Reporting and recordkeeping requirements.

Dated: May 7, 1985.

J.A. Moore,

Assistant Administrator for Pesticides and Toxic Substances.

PART 799—[AMENDED]

40 CFR Part 799 is amended as follows:

1. The authority citation for Part 799 is revised to read as follows:

Authority: 15 U.S.C. 2603, 2611, 2625.

2. Part 799 is amended by adding § 799.2175 to Subpart B to read as follows:

§ 799.2175 C9 aromatic hydrocarbon fraction.

(a) *Identification of chemical substance.* The C9 aromatic hydrocarbon fraction obtained from the reforming of crude petroleum shall be tested in accordance with this Part.

(b) *Identification of test substance.* A C9 substance consisting of *ortho-*, *meta-* and *para*-ethyltoluene (minimum 22 percent), and 1,2,4-, 1,2,3,- and 1,3,5-trimethylbenzene minimum 15 percent) that is representative of a typical C9 aromatic hydrocarbon fraction obtained from the reforming of crude petroleum (minimum total ET–TMB content 75 percent) and intended for use as a solvent end product shall be prepared and used as the test substance in all tests.

(c) *Persons required to submit study plans, conduct tests and submit data.* All persons who manufacture or process, or intend to manufacture or process, the C9 aromatic hydrocarbon fraction, other than as an impurity, from July 1, 1985, to the end of the reimbursement period shall submit letters of intent to test, exemption applications, and study plans, and shall

conduct tests and submit data as specified in this section, Subpart A of this part, and Part 790 of this chapter.

(d) *Health Effects Testing*—(1) *Mutagenic effects—Chromosomal aberrations*—(i) *Required testing.* (A) An in vitro cytogenetics test shall be conducted with the C9 test substance.

(B) An in vivo cytogenetics test shall be conducted for the C9 test substance if the in vitro cytogenetics test conducted pursuant to paragraph (d)(1)(i)(A) of this section produces a negative result.

(C) A dominant lethal assay shall be conducted with the C9 test substance unless the in vitro cytogenetics test conducted pursuant to paragraph (d)(1)(i)(A) of this section and the in vivo cytogenetics test conducted pursuant to paragraph (d)(1)(i)(B) of this section (if required) produce negative results.

(D) A heritable translocation assay shall be conducted with the C9 test substance if the dominant lethal assay conducted pursuant to paragraph (d)(1)(i)(C) of this section produces a positive result.

(ii) *Study plans.* For guidance in preparing study plans, it is recommended that the OTS Health Effects Test Guidelines for Chromosomal Effects, published by NTIS (PB 83–257691), be consulted. Additional guidance may be obtained from the OECD Test Guidelines for Health Effects-Genetic Toxicology, published by OECD, and the Pesticide Assessment Guidelines: Subdivision F, published by NTIS (PB 83–153916).

(2) *Mutagenic effects—Gene mutation*—(i) *Required testing.* (A) A *Salmonella typhimurium* mammalian reverse mutation microsomal assay shall be conducted with the C9 test substance, both with and without activation.

(B) A sister chromatid exchange (SCE) assay shall be conducted with the C9 test substance.

(C) A gene mutation in mammalian cells in culture assay shall be conducted with the C9 test substance.

(D) A second gene mutation in mammalian cells in culture assay, using a different cell line from that used in the first assay, shall be conducted with the C9 test substance if the first gene mutation in cells in culture assay, conducted pursuant to paragraph (d)(2)(i)(C) of this section, produces a negative result, unless the *Salmonella* microsomal assay, conducted pursuant to paragraph (d)(2)(i)(A) of this section, and the SCE assay, conducted pursuant to paragraph (d)(2)(i)(B) of this section, produce negative results.

(E) A *Drosophila* sex-linked recessive lethality test shall be conducted with the C9 test substance unless the *Salmonella* microsomal assay conducted pursuant to paragraph (d)(2)(i)(A) of this section and the gene mutation in cells in culture assays conducted pursuant to paragraphs (d)(2)(i) (C) and (D) of this section produce negative results.

(F) A mouse specific locus assay shall be conducted with the C9 test substance if the *Drosophila* sex-linked recessive lethality test, conducted pursuant to paragraph (d)(2)(i)(E) of this section produces a positive result.

(ii) *Study plans.* For guidance in preparing study plans it is recommended that the OTS Health Effects Test Guidelines for Gene Mutations and DNA Effects, published by NTIS (PB 83–257691 and PB 84–233295), be consulted. Additional guidance may be obtained from the OECD Test Guidelines for Health Effects-Genetic Toxicology, published by OECD, and the Pesticide Assessment Guidelines: Subdivision F, published by NTIS (PB 83–153916).

(3) *Oncogenicity*—(i) *Required testing.* A 2-year inhalation oncogenicity bioassay shall be conducted with the C9 test substance unless it produces negative results in all of the following tests: In vitro cytogenetics test, in vivo cytogenetics test (if required), first gene mutation in cells in culture assay, second gene mutation in cells in culture assay (if required), and *Drosophila* sex-linked recessive lethality test (if required) conducted pursuant to paragraphs (d)(1)(i) (A) and (B) and (d)(2)(i) (C), (D) and (E) of this section.

(ii) *Study plans.* For guidance in preparing study plans, it is recommended that the OTS Health Effects Test Guidelines for Chronic Exposure-Oncogenicity published by NTIS (PB 83–257691), be consulted. Additional guidance may be obtained from the OECD Test Guidelines for Health Effects Section 451, published by OECD, and the Pesticide Assessment Guidelines: Subdivision F, published by NTIS (PB 83–153916).

(4) *Developmental Toxicity*—(i) *Required testing.* An inhalation developmental toxicity study shall be conducted with the C9 test substance.

(ii) *Study plans.* For guidance in preparing study plans, it is recommended that the OTS Health Effects Test Guideline for Inhalation Development Toxicity Study Teratogenicity, published by NTIS (PB 84–233295), be consulted. Additional guidance may be obtained from the OECD Test Guidelines for Health Effects, and the Pesticide Assessment Guidelines: Subdivision F, published by NTIS (PB 83–153916).

(5) *Reproductive Effects*—(i) *Required testing.* An inhalation reproductive effects study shall be conducted with the C9 test substance.

(ii) *Study plans.* For guidance in preparing study plans it is recommended that the OTS Health Effects Test Guidelines for Specific Organ/Tissue Toxicity-Reproduction and Fertility Effects, published by NTIS (PB 83–257691), be consulted. Additional guidance may be obtained from the OECD Test Guidelines for Health Effects Section 416, published by OECD, and the Pesticide Assessment Guidelines: Subdivision F, published by NTIS (PB 83–153916).

(6) *Neurotoxicity*—(i) *Required testing.* A neurotoxicity test battery consisting of a 90-day subchronic inhalation exposure incorporating the following tests shall be conducted with the C9 test substance:

(A) A neuropathology test;

(B) A motor activity test; and

(C) A functional observation battery.

(ii) *Study plans.* For guidance in preparing study plans it is recommended that the OTS Health Effects Test Guidelines for Neurotoxicity, published by NTIS (PB 83–257691), be consulted.

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